Biology of ageing

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Unravelling the basic mechanisms of ageing is a pre-requisite for developing appropriate means of relieving age-related conditions in the elderly. The physiological changes that occur with ageing originate in the molecular biology of cells and contribute not only to normal human ageing but also to age-related pathologies. An urgent priority, therefore, if we are to intervene in age-related pathologies, must be to understand how different cell types alter during ageing and how these alterations interact to produce pathobiological effects. **T.B.L. Kirkwood** (University of Newcastle, UK) focused on the intrinsic variability of individual aspects of the senescent phenotype: chance operates at all levels during development and ageing of the organism making predictions about indivduals' ageing processes difficult. He emphasized the need to consider the multiple processes that contribute collectively to tissue ageing, a fact that was also stressed by **C. Franceschi** (University of Bologna, I) with particular respect to the immune system. One general feature, however, is replicative senescence of cells. **J. Campisi** (Lawrence Berkeley Laboratory, USA) presented preliminary data suggesting that preneoplastic epithelial cells are more likely to express neoplastic properties if they are in contact with senescent stromal cells.

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Several talks dealt with the fact that cell stress has many important connections with cellular ageing. **O. Toussaint** (University of Namur, B) presented preliminary data suggesting that Transforming Growth Factor-β1 (TGF-β1) mediates the appearance of stress-induced premature senescence (SIPS) in human normal fibroblasts after sublethal H_2O_2 stress. SIPS represents an ideal system for testing the long-term effects of exposure of human cells to sublethal concentrations of various molecules developed for industrial purposes. Data from proteome and transcriptome analyses suggest that SIPS not only shares changes in gene expression with normal senescence, but is also characterized by specific changes in gene expression—the 'molecular scars' of stress.

Another form of cellular stress involves radiation effects. Premature terminal differentiation of early passage skin fibroblasts is induced by ionising radiation. Furthermore, the risk of developing radiation-induced subcutaneous fibrosis may be correlated with the differentiation state prior to irradiation (**C. Herskind**, University of Tübingen, G).

P. Pelicci (Istituto Europeo di Oncologia, Milan, I) showed that mouse p66shc protein regulates stress-related apoptotic responses and that targeted mutation of p66shc reduces the oxidative stress response and extends lifespan in mouse. **S.I.S. Rattan** and **B.F.C. Clark** (University of Aarhus, DK) proposed that repeated doses of very mild heat stress might promote hormesis (the benificient effect of exposure to such stresses) through prevention of the first steps of replicative senescence.

The small heat-shock proteins (sHsp) protect cells against heat shock and oxidative stress. Several downstream effects resulting from increased intracellular levels of reactive oxygen species (ROS) are diminished by sHsp expression, such as NF-κB activation. The anti-apoptotic effects of sHsp seem to work both upstream of cytochrome c release and downstream at the level of caspase 3 activation (**A.-P. Arrigo**, University of Lyon, F). The protein clusterin was shown by **E.S. Gonos** (NHFR, Athens, GR) and **O. Toussaint** (University of Namur, B) to increase cell survival in stressful conditions.

DNA damage is one major form of cellular damage that has been implicated in the ageing process. Telomere shortening may be one indicator of such damage. **T. von Zglinicki** (University of Newcastle, UK) showed new data suggesting that telomere length, previously shown by his

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group to be strongly affected by oxidative stress, might serve as an independent and robust parameter for assessing the risk of vascular dementia and, possibly, other age-related degenerative diseases. **G. Butler-Browne** (University of Paris VII, F) showed a correlation decreased proliferative lifespan and telomere length in human muscle satellite cells which is especially significant in Duchenne muscular dystrophy.

The Werner Syndrome or WRN protein, whose deficiency dramatically accelerates ageing, may have properties that allow it to sense the presence of damage in DNA. **V.A. Bohr** (N.I.A., Baltimore, USA) reported on new proteins that show physical and functional interactions with WRN. **A. Bürkle** (University of Newcastle, UK) provided evidence that poly (ADP-ribose) polymerase-1 (PARP-1) is a key regulator of alkylation-induced sister chromatid exchanges, tuning the rate of genomic instability events to a level that is just appropriate for the longevity potential of a given species.

Protein turnover is an important mechanism for cells to cope with aberrant proteins. In keratinocytes and epidermal cells subjected to serial passaging, there is an inverse relationship between senescence-associated β-galactosidase activity and proteasome content (**B. Friguet**, University of Paris, F). The observed decline in proteasome activity with age may also be related to alterations of its subunits, as suggested by determination of purified proteasome peptidase specific activities that were found to exhibit an age-related decrease. **T. Grune** (Charite Berlin, G) demonstrated that oxidized proteins accumulate during cell senescence, possibly due to an overall decrease in protein turnover.

The role of mitochondria bioenergetics in ageing is also currently attracting much attention. During oxidative phosphorylation, some of the redox energy in substrates is lost as heat. This uncomplete coupling is mostly due to natural leakage of protons across the mitochondrial inner membrane. **M. Brand** (University of Cambridge, UK) estimated that mitochondrial proton cycling is responsible for 20–25% of basal metabolic rate in rats. An attractive candidate for the function of the universal and expensive energy-dissipating proton cycle is to decrease the production of ROS. Certain mutant strains of yeast are able to cope with mtDNA damage by activating a suitable nuclear response and increasing lifespan. **M. S. Jazwinski** (Louisiana State University, USA) described the current understanding of this compensatory mechanism, which is known as the Retrograde Response (RR). It is modulated by the longevity gene *RAS2* and adjusts the activity of nuclear genes and longevity to the strength of a signal generated by the mitochondrion. In humans, an increase in both somatic mtDNA mutations and germ-line inherited mtDNA variants are associated with ageing and longer life-spans. As some stress-responder genes are specifically associated with human longevity, **G. De Benedictis** (University of Calabria, I.) suggested that RR may also be present in mammals.

Caloric restriction is also known to increase life-span in certain animal model systems. **G. Roth** (N.I.A., Baltimore, USA) is exploring agents that might elicit the same beneficial effects produced by caloric restriction on mammalian lifespan but without dieting. One candidate is 2-deoxyglucose, a sugar analog with a limited metabolism, which actually reduces glucose/energy flux without decreasing food intake in rats. Doses were titrated to eliminate toxicity; a long-term longevity study is now underway.

H.D. Osiewacz (Goethe University, Frankfurt, G) described the characterization of the nuclear gene *Grisea* which codes for a copper-modulated transcription factor (GRISEA) involved in the tight control of copper homeostasis in the filamentous ascomycete *Podospora anserina*. Low cellular copper found in long-lived mutant *Grisea* has an impact on mitochondrial energy transduction. In this mutant, an alternative cyanide-resistant pathway is induced and the mtDNA is stabilized. As a consequence, mitochondrial oxidative stress is lower, and lifespan is extended.

"Age" mutants increase the ability of the worm *Caenorhabditis elegans* to withstand a variety of stresses. The role of the Age genes in both longevity and stress resistance indicates that a major evolutionary determinant of longevity is the ability to respond to stress (**T. Johnson**, University of Colorado, USA). Mutants in the insulin signalling pathway also extend lifespan in *C. elegans*. This signalling pathway is involved in the alternative developmental pathway leading to formation of the long-lived, stress-resistant dauer larva, which is produced in response to reduced food supply.

In the fruitfly *Drosophila melanogaster*, mutants have been made in genes that encode components of the insulin signalling pathway, initially to study the role of this pathway in control of growth during the pre-adult period. **L. Partridge** (UC London, UK) described screening these mutants for effects on lifespan and found that one of them, *chico*, extends adult lifespan in both sexes.

The meeting concluded with several talks on age-related neurodegenerative diseases in humans and mammalian models. **H.M. Schipper** (McGill University, Canada) observed that heme oxygenase-1 (HO-1) immunoreactivity is greatly enhanced in neurons and astrocytes of the hippocampus and cerebral cortex of Alzheimer subjects and that it co-localizes to senile plaques and neurofibrillary tangles. HO-1 staining is also augmented in astrocytes and "decorated" neuronal Lewy bodies in the Parkinson substantia nigra. Paradoxically, HO-1 mRNA levels are markedly suppressed in peripheral lymphocytes of patients with early sporadic Alzheimer disease and may thus provide a biomarker of the early stages of this condition.

Alterations in both iron storage and glutathione levels in the substantia nigra have been correlated with the neuronal

degeneration accompanying Parkinson disease. A direct causative role definitively proved in vivo is being investigated by **J.K. Andersen** (University of Southern California, USA), using genetically engineered cells and transgenic animals.

The amyloid peptide (Aβ) is the major constituent of the amyloid core of senile plaques found in the cerebral cortex of patients with Alzheimer. Aβ is derived from the amyloid precursor protein or APP. **F. Van Leuven** (K.U. Leuven, B.) showed that ageing caused accumulation of massive amounts of plaque-precipitated amyloid peptides, related to failure to clear and/or degrade the amyloid peptides in the brain of ageing APP/Lo transgenic mice. **P. Kienlen-Campard** (Catholic University of Louvain, Brussels Campus, B.) presented data suggesting that neuronal loss is related to intraneuronal processing of APP.

The proceedings of this meeting will be published in *Experimental Gerontology* in September 2000. A critical mass for rapid progress in molecular gerontology now exists in terms of individual knowledge, know-how, and efficient networking. The latter has been made possible, in part by support from the European Union such as the concerted-action 'Molgeron'. The excellence of this networking will be sustained through the second Euroconference on the Biology of Ageing to be held in Greece (18–22 May 2002, chairman: Dr. **E.S. Gonos** [sgonos@eie.gr]).